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FUNCTIONAL TESTS IN THE STUDY OF WATER-SALT EXCHANGE AND RENAL FUNCTION IN COSMONAUTS

by

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Short-term and prolonged manned space flights have evoked significant altera- /1*
tions in the state of water-salt exchange and renal activity. This has been related to the influence of a large number of factors, the specific significance of each of which is difficult to measure individually. G-forces and stress, zero-gravity, and alterations in biorhythms have led to an alteration in the neuro-psychic state, endocrine status, hemodynamics, and redistribution of fluid phases. This, in turn, might create other conditions for renal function — the basic effector of the functional system, which maintains constancy in the volume, ion composition, and osmotic concentration of fluids of the inner body.

Studies of water-salt exchange and renal function in cosmonauts have received much attention in both the Soviet and American programs. The results of investigations performed during training and the performance of flights aboard individual craft and the generalization of the data obtained have been discussed at a number of conferences and symposiums (Refs. 1—3). In these works, data were summarized concerning the ion content of the blood and urine of cosmonauts and the characteristics of the function of their kidneys before flight and after its completion, as well as in a number of cases during flight. Our report involves analysis of the results of studying renal function during the application of loading tests.

The kidney is an organ with very great reserve capabilities. Experiments on animals and clinical experience indicate that in normal conditions, removal of one kidney and resection of part of the second kidney do not disrupt water-salt homeostasis, as long as the remaining part of the kidney fully provides the elimination of excess water, salts, and nitrogen-metabolism products. The kidney, depending on the state of fluid balance, can alter the ecretion of urine by dozens of times, /2
and similarly can regulate salt excretion as well. Therefore, to evaluate the

* Numbers in the margin indicate pagination in the foreign text.

state of the kidneys and their regulation systems in experiments and in clinical practice, functional-load tests are always used, as is the Folhardt test, the test with bicarbonate load, and many others.

In connection with this, the Soviet program for the examination of cosmonauts and experimenters included the study of the state of the kidneys and their regulation both for various forms of their occupational activity, and in conditions of the application of tests aimed specially at the analysis of the renal functional capability. Much attention has been devoted particularly to the test with water administration. If water and electrolyte excretion are unchanged after the water load, this indicates that the osmoreceptors are reacting adequately, secretion of the antidiuretic hormone (ADH) has ceased, and glomerular filtration and canalicular reabsorption of each of the ions are proceeding at the required level. Measurement of the maximum concentration capability of the kidneys before the water test makes it possible to evaluate the level of ADH secretion and the efficiency of cellular mechanisms of reaction to this hormone.

The alteration in circadian excretion of water and salts in Soviet cosmonauts is quite similar to that which was found in the American astronauts (Refs. 4-10). The small differences probably were related to features of the work performed, flight duration, nutrition conditions, and the spacecraft cabin atmospheric composition. Sodium concentration in blood serum and its osmotic concentration immediately after landing were somewhat higher than during the initial period. Potassium and calcium concentration was practically unchanged (Table 1). In comparison with the pre-launch period, during the first days after completion of the flight, excretion of water, sodium, and potassium decreased (Table 2). Under /4
ground conditions, the body reacts to the weight loss related to the excess excretion of water and salts during flight by an adequate retention of fluids and electrolytes (Table 3). Analysis of the relationship between diuresis and osmotic concentration of urine indicated significant differences between these indices

TABLE 1

ELECTROLYTE CONTENT (MILLIEQUIVALENT/LITER) AND OSMOTIC CONCENTRATION (MOSM/L) IN BLOOD SERUM OF COSMONAUTS BEFORE FLIGHTS (1) AND AFTER FLIGHTS (2)

INITIALS (Last, ~~Middle,~~ First) Middle)	Sodium		Potassium		Calcium		Chlorine		Osmotic Concentration	
	1	2	1	2	1	2	1	2	1	2
1. K. V. N.	148	155	5.1	7.0	-	-	-	-	285	311
2. F. K. F.	147	147	5.1	6.1	-	-	-	-	306	311
3. Ye.B. B.	148	143	5.1	6.9	-	-	-	-	311	311
4. B. G. T.	145	148	4.0	3.7	4.6	5.0	110	105	304	310
5. Sh.V. A. (I)	139	-	5.1	5.65	5.0	5.0	100	103	304	311
6. V. B. V.	139	144	3.9	3.7	5.0	4.6	96	96	300	303
7. Ye.A. S.	139	152	4.1	4.15	4.6	5.0	98	100	302	308
8. Kh.Ye.V.	139	144	4.1	4.15	4.8	4.8	96	98.5	301	305
9. Sh.G. S.	137	139	4.1	3.9	4.6	5.4	110	104	290	294
10. K. V. N.	140	145	4.0	4.0	4.7	5.9	98	104	294	298
11. F. A. V.	139	143	5.0	4.8	4.1	4.4	100	104	295	303
12. V. V. N.		139	-	5.1	-	4.8	-	100	-	-
13. G. V. V.	135	139	4.5	4.1	4.5	4.8	96	99	290	295
14. Sh.V. A. (II)	148	150	3.8	3.85	4.7	4.4	98	98	301	299
15. Ye.A. S. (II)	139	139	4.0	4.2	4.8	4.4	95	102	300	294
16. N. A. G.	152	143	5.0	4.0	4.4	4.9	-	-	302	303
17. S. V. I.	147	143	5.9	4.5	5.2	5.25	-	-	298	301
18. L. V. G.	147	135	4.5	4.4	6.0	7.2	-	-	294	298
19. M. O. G.	152	135	4.5	4.6	5.6	5.6	-	-	300	[illegible]
M	142	145	4.5	4.7	4.7	4.9	99	101	298	304
±M	1.27	1.2	0.16	0.26	0.08	0.11	1.5	0.82	1.7	1.44

I - Flight of V. A. Shatalov and A. S. Yeliseyev in January, 1969.

II - Flight of V. A. Shatalov and A. S. Yeliseyev in October, 1969.

TABLE 2

ELIMINATION OF FLUID (ML), ELECTROLYTES (MILLIEQUIVALENTS), AND OSMOTICALLY ACTIVE SUBSTANCES (MOSM) BEFORE FLIGHT (1) AND DURING THE FIRST DAYS AFTER FLIGHT (2)

INITIALS (Last, First) Middle	Diuresis		Sodium		Potassium		Calcium M		Osmotically Active Substances	
	1	2	1	2	1	2	1	2	1	2
1. B. G. T.	740	600	55	34	56	28	6.5	6.2	832	490
2. Sh.V. A. (I)	1020	645	142	118	52	35	9.8	9.6	1030	660
3. V. V. V.	840	1065	169	176	43	54	8.4	9.4	920	918
4. Ye.A. S. (I)	700	1000	194	165	40	51	8.4	11.6	830	874
5. Kh.Ye.V.	1200	1030	220	206	74	58	10.2	11.5	1130	814
6. Sh.G. S.	890	880	179	144	44	37	3.3	21.9	928	726
7. K. V. N.	950	705	165	116	58	35	8.4	17.8	965	680
8. F. A. V.	1400	655	230	109	90	39	9.0	9.3	1260	585
9. V. V. N.	955	590	140	71	50	26	5.4	7.1	850	672
10. G. V. V.	985	730	147	97	49	31	9.4	8.6	958	665
11. Sh.V. A. (II)	1015	580	145	88	40	39	9.0	4.6	1000	470
12. Ye.A. S. (II)	1180	875	195	102	50	42	8.0	11.1	1134	754
13. N. A. G.	1125	690	266	104	55	26	9.3	11.3	915	666
14. S. V. I.	1185	660	230	126	71	31	13.7	10.8	1070	616
M	1013	765	176.9	118.3	55.1	38	8.5	10.8	987	685
±M	51.4	45.6	13.9	11.8	3.8	2.7	0.64	1.19	33.6	34.3

I - Flight of V. A. Shataiov and A. S. Yeliseyev in January, 1969.

II - Flight of V. A. Shatalov and A. S. Yeliseyev in October, 1969.

TABLE 3

DYNAMICS OF CHANGE IN BODY WEIGHT OF COSMONAUTS AFTER FLIGHT

Spacecraft	Flight Duration (days)	Name of Cosmonaut	Change in body weight in comparison with original on day of launch (kg)			
			at place of landing	after flight (1 day)	before water loading	after water loading
Soyuz-4	3	V. A. Shatalov	-3.9	-0.2	0	+0.2
Soyuz-5	3	B. V. Volynov	-2.4	-1.5	-0.1	+0.8
Soyuz-4, 5	2	Ye. V. Khrunov	-1.9	-0.7	-0.2	+0.5
Soyuz-4, 5	2	A. S. Yeliseyev	-2.0	-2.0	-1.5	+0.5
Soyuz-6	5	G. S. Shonin	-2.5	-1.5	-1.4	+0.1
"	5	V. N. Kubasov	-2.1	-0.9	-0.7	+0.2
Soyuz-7	5	A. V. Filipchenko	-3.9	-2.1	-1.8	+0.3
"	5	V. V. Gorbatko	-2.0	-0.8	-0.8	0
"	5	V. N. Volkov	-2.4	-0.6	-1.3	-0.7
Soyuz-8	5	V. A. Shatalov	-2.2	+0.2	+0.2	0
Soyuz-8	5	A. S. Yeliseyev	-3.6	-1.6	-1.3	+0.3
Soyuz-9	18	A. G. Nikolayev	-2.7	-1.3	-1.3	0
"	18	V. I. Sevast'yanov	-4.0	-2.3	-2.4	0
Soyuz-12	2	V. G. Lazarev	-3.1	-1.9	-1.8	+0.1
"	2	O. G. Makarov	-2.0	-0.9	-0.8	+0.1

after flight (Fig. 1). The cosmonauts' diuresis during the first days after flight was lower, while the osmotic concentration of urine was lower (and not higher), i.e., the normal relationships between diuresis and urine concentration were distorted. This might be related to the fact that electrolyte retention exceeds water retention in the body.

Detailed analysis of the state of the individual functions of the kidneys can be performed by means of functional tests. The test with water load was normally performed 36 to 40 hours after landing, i.e., at the time when body weight in most cosmonauts approximated the pre-flight weight (Table 3); they no longer experienced the feeling of thirst, and the acute state of stress after the craft landed had passed. The results of the tests carried out proved unambiguous in most cosmonauts who had made flights with a duration of 1 to 5 days. In crewmembers of the "Voskhod" and "Soyuz" craft, water excretion after the water load was sharply decreased as a result of a decrease in the kidneys' capability for osmotic extraction of urine. Comparison of canalicular filtration, osmotic clearance and the concentration capability of the kidneys (Fig. 2) made it possible, after the flight of "Voskhod" craft as early as 1964, to propose (Ref. 7) that an alteration in the activity of the renal regulation systems, including increased ADH secretion, after return to earth is a compensatory reaction to the excess loss of extracellular fluid during the first days of stay in space. On the basis of these data, including the results of the last flight of the "Soyuz-12," it is possible to assume that readaptation after a stay in zero-gravity is not completed in the first day after return, and the water test catches those shifts in the state of the regulation system which are not revealed either by the data based on daily urine by the urine content (Table 2).

First of all, it is necessary to analyze the causes for the altered reaction to the water load. Glomerular filtration, measured on the basis of clearance of creatinine, did not differ in the cosmonauts from the pre-flight values in either

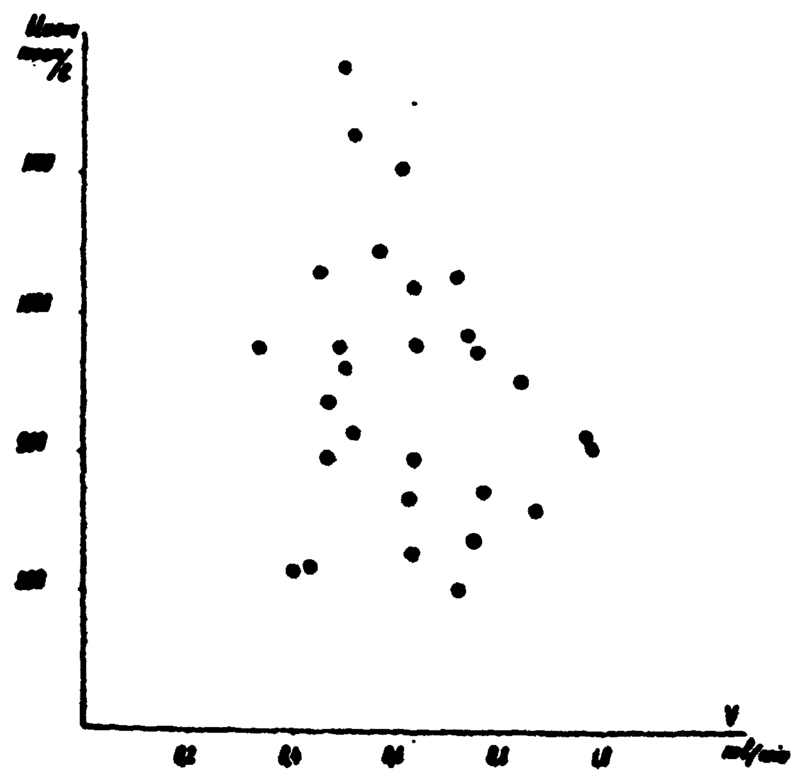

Fig. 1. Relationship between osmotic concentration of urine (Uosm) and amount of urination (V) in daily urine tests

O --- before flight

● --- after flight

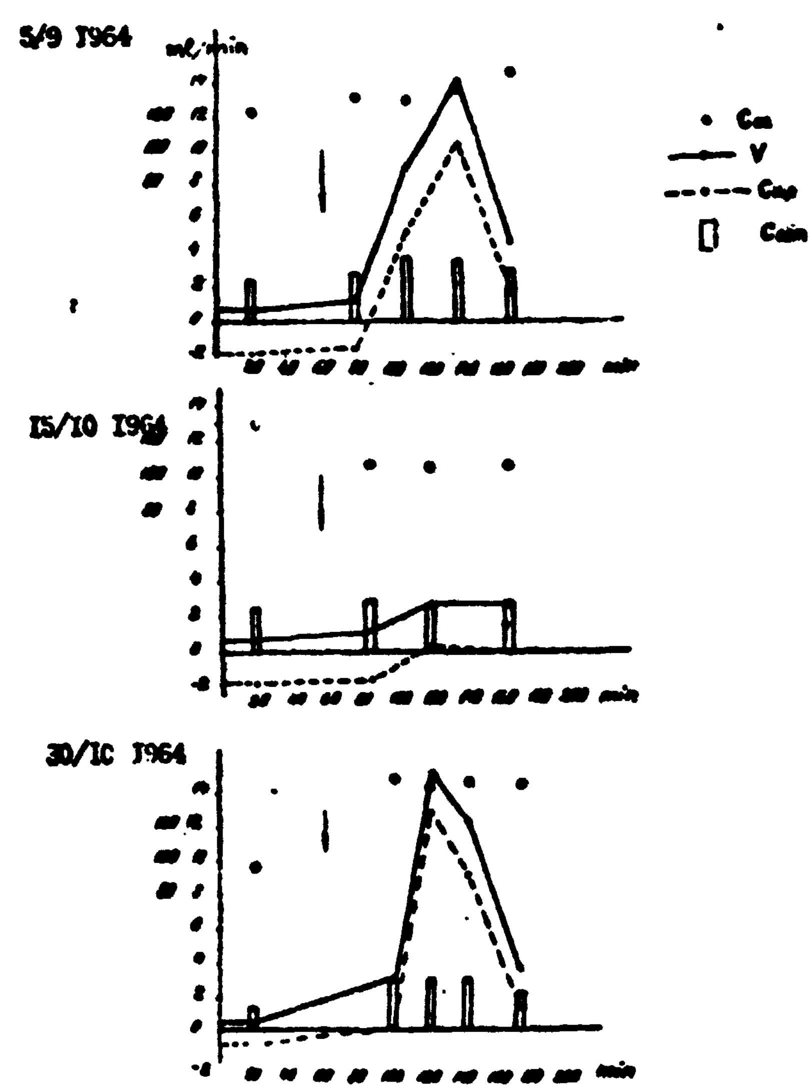

Fig. 2. Indices of the functional state of the kidneys in testing V. Komarov with water load before and after flight.

Before flight --- 9/5 1964

After flight --- 10/15 1964; 10/30 1964

the period of 12 hours of water deprival before the water load or during a sharp increase in diuresis after drinking water (Figs. 2 and 3). Consequently, the cause of the decreased water diuresis [lies] in the increased canalicular reabsorption of water. A basic factor in the regulation of the osmotic permeability of the canalicular wall is ADH. Permeability of the canalicular wall can increase due to an insufficient level of corticosteroids, hypocalcemia, etc. Data from examinations of Soviet cosmonauts make it possible to exclude both these factors as a cause of decreased excretion of the water load. During the water load, excretion of 17-hydroxycorticosteroids after flight not only does not decrease, but even increases by comparison with pre-flight values (Ref. 5). The concentration of calcium in the blood also remains at the level of the pre-flight values and cannot be considered a cause of the increased permeability of the canalicular wall. Consequently, it remains to be concluded that either the water load in the post-flight period does not lead to complete suppression of ADH secretion, or the activity of renal cells is altered. In order to experimentally analyze these possibilities, the renal capacity for osmotic concentration of urine was investigated in the cosmonauts. Starting from the evening [before], the subjects received no water or food, and the morning portion of urine prior to the water load was analyzed. Its osmotic concentra- /11
tion was as high as before the flight (Fig. 4). This makes it possible to consider that the combined activity of all portions of the nephron, the vessels, and the extracellular metabolism of the components which constitute the kidney remains undisrupted. Consequently, alterations in the activity of the kidney after flight can be explained by an alteration in the activity of the regulation system.

In most cosmonauts, the excretion of water after water load was lowered (Table 4). The question arises as to what causes the drop in the excretion of osmotically free water at the maximum of diuresis after the water load -- an increase in the permeability of the wall of the distal canaliculus for water or a decrease in reabsorption of salts, primarily sodium, and the increase in the osmotic concentra-

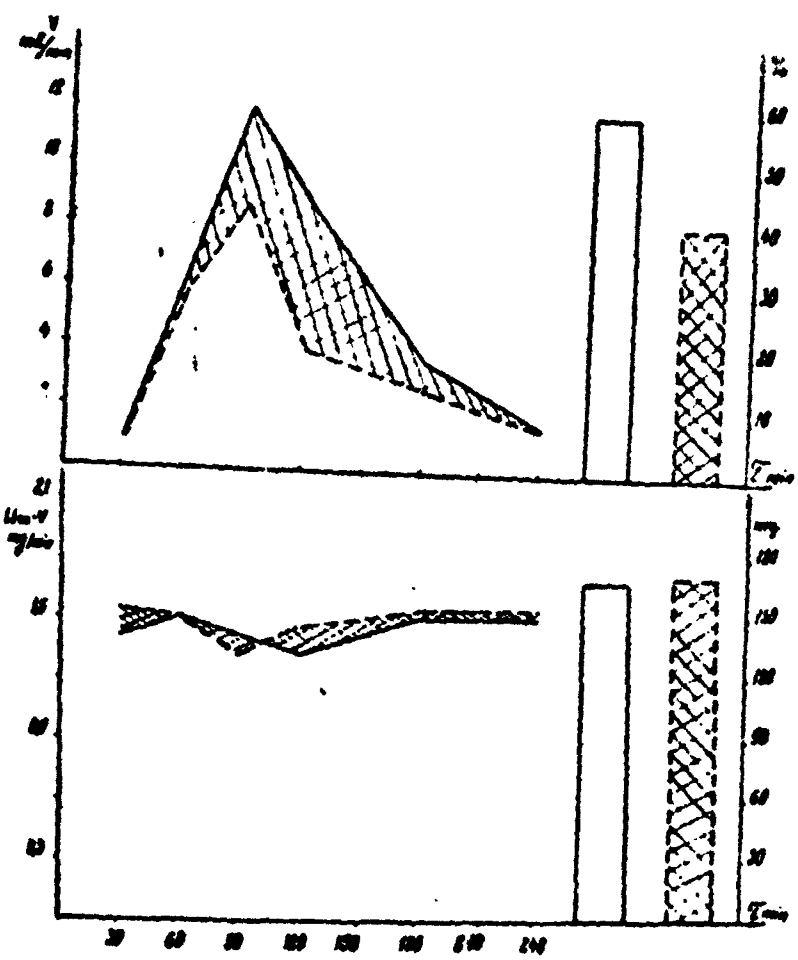

Fig. 3. Elimination of liquid and creatinine by kidneys during test with water load. Columns: excretion of fluid and creatinine two hours after administration of water.

——— - before flight --

- - - - - after flight --

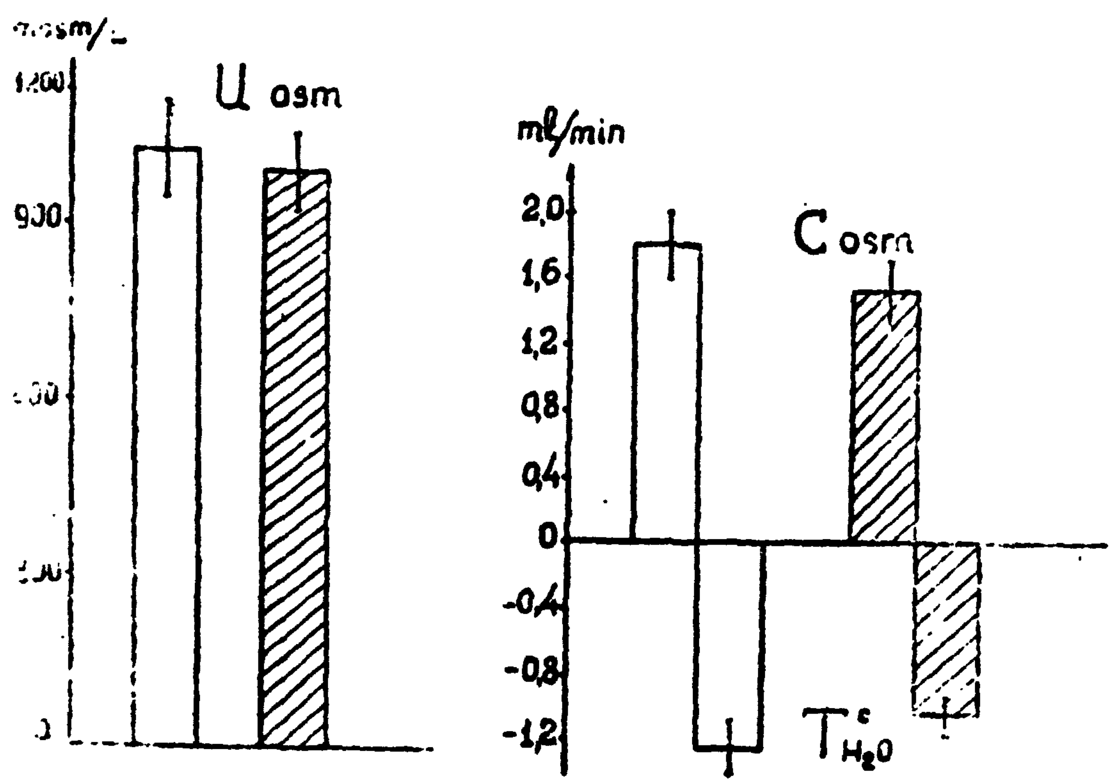

Fig. 4. Indices of the osmoregulating function of the kidneys after 12 hours of deprivation of food and water.

☐ -- before flight
▨ -- after flight

tion of urine which is conditioned by this. It was found that there is observed not only a decrease in the excretion of water at the maximum of water diuresis, but also an increase in its osmotic concentration (Table 4). This might be explained by an increase in the absorption of water at the end portions of the canaliculi. However, there is observed not only an increase in the concentration of sodium and the osmolarity of these urine tests, but also an increase in the excretion of sodium (but not potassium) during the water test (Fig. 5). This may depend on the decrease in the distal reabsorption of sodium. The difference between the functioning of the regulation system of the water (osmotic) and sodium balance becomes particularly clear in those cosmonauts whose kidneys retained the capability for a normal rate of fluid excretion at the maximum of diuresis (A. G. Nikolayev, V. N. Kubasov and various others).

The data presented in Figure 6 show that in V. N. Kubasov the dynamics of the excretion of the water load in conditions of pre- and post-flight examination were similar. However, the clearance of osmotically active substances and the excretion of certain ions, particularly sodium and calcium, is substantially higher after /16 flight. Under normal circumstances, to maintain homeostasis after excessive introduction of water into the organism, the excretion of salts does not change or decrease; in cosmonauts after flight, on the other hand, it rises. Thus, the results of the water test in cosmonauts after landing indicate incomplete suppression of ADH secretion (one cannot exclude the activity of other factors as well, which increase the cells' sensitivity to ADH) and the lowering of the reabsorption of sodium and calcium in the terminal sections of the canaliculi.

At the present it is difficult to name the concrete physiological mechanisms which cause a lowering of the reabsorption of sodium and calcium ions in the distal segment of the nephron. It can be supposed that after flight under conditions of water load, mismatching can be revealed in the activity of the water and salt exchange regulation system. The introduction of a fluid with the water load in

TABLE 4

FUNCTIONAL STATE OF KIDNEYS IN COSMONAUTS IN THE PERIOD BEFORE AND AFTER FLIGHT RESEARCH ($M \pm m$)

	Voskhod, Soyuz-3, -4, -5, -6, -7, & -12		Soyuz-8 (repeat flight)		Soyuz-9	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
Elimination of fluid (in % of ingested)						
in 2 hours	67±5.65	44.5±5.1	65±0	64.5±0.5	59±9.0	85±0
in 4 hours	90.4±4.7	51.7±4.3	129±12	91.5±0		
Maximal diuresis (ml/min)	14.6±0.41	9.24±0.91	16.0±0.65	15.05±0.95	8.9±1.9	10.15±1.15
Concentration in urine in maximum diuresis						
Sodium (milliequiv/l)	11.7±1.2	18.0±3.64	10.5±1.0	11.5±3.5	14.0±6.7	10.4±1.9
Potassium (milliequiv/l)	7.12±0.77	10.43±2.53	6.0±0.3	5.6±0.6	6.0±5.7	4.6±1.1
Calcium (milliequiv/l)	0.6±0.07	1.83±0.97	0.98±0.13	0.42±0.14	1.2±0.8	0.9±0.2
Osmotically active substances (mosm/l)	65.6±2.97	145±16.1	53.5±1.5	76.5±10.5	84±8.0	73.5±0.5
Excretion of osmotically free water in maximum diuresis (ml/min)	11.6±0.43	5.65±0.87	13.2±0.45	11.2±1.2	6.46±1.6	7.69±0.85

Fig. 5. Dynamics of excretion of sodium and potassium during test with water load. Columns: excretion of potassium and sodium two hours after administration of water.

______ - before flight

\- - - - - after flight

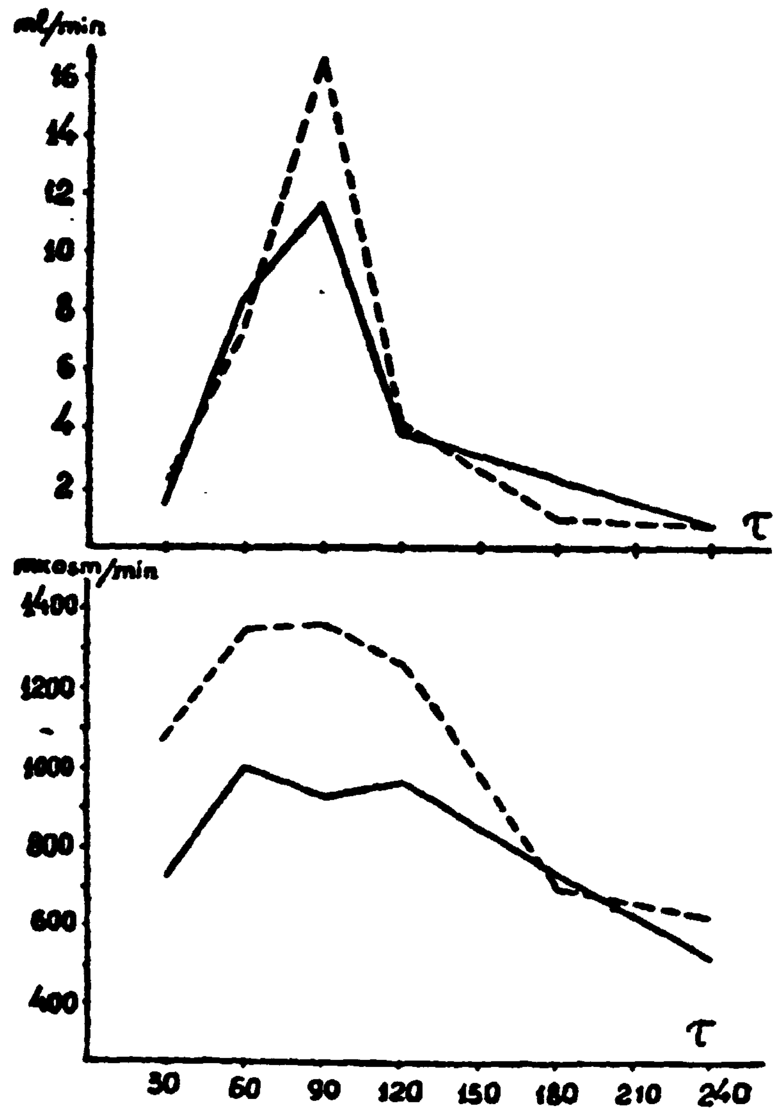

Fig. 6. Excretion of water and osmotically active substances by kidneys after water load in V. Kubasov

——— - before flight

- - - - - after flight

a still-unstabilized hemodynamics probably can be taken as a necessity for the excretion of excess intravascular fluid -- and its basic components -- water, sodium and chlorine. Under normal situations, information from the osmoreceptors and possibly also from the recently described specific sodium receptors allows the regulation systems to differentiate whether the increase in volume is connected only with the introduction of water or whether water with sodium has been introduced into the organism. In the case observed by us, this does not take place in full volume, and the dysbalance of the regulation systems is reflected in an increased sodium uresis only against the background of water diuresis (fig. 7)

One of the ways of analyzing the causes of change in the water-isolating and sodium-uretic function of the kidneys in cosmonauts could be the study of these processes in experiments with simulation of separate flight factors. In investigations on subjects (Ref. 11) it was shown that transverse accelerations do not cause protracted changes in the osmoregulatory function of the kidneys. In dogs on the day following acceleration activity, the excretion of water and osmotic concentration remain the same as in the initial period (Ref. 12 /18

Another flight factor -- weightlessness -- can be reproduced partially under conditions of ground experiments with hypokinesia (Refs 13, 14). An examination was performed on four groups of subjects (six persons each) (Table 5). One group was left in a free regimen, and three in a horizontal position in bed with various angles of inclination of the top half of the body -- +6°, -2°, and -6°. In carrying out the water test during hypokinesia, reliable differences were not observed in the separation of water, maximal water diuresis and excretion of sodium. After 30 days of the bed [rest] regimen, the subjects were tested on the second [? -- illegible] and ninth days of stay in conditions of normal motor activity. On the second day during the water test, excretion of sodium was sharply lowered, with a slight tendency to retain water, i.e., a qualitatively different response was observed in relation to sodium than had been the case with the cosmonauts. It can

TABLE 5

ELIMINATION OF FLUID (IN % OF THAT INGESTED), SODIUM, AND POTASSIUM (IN MILLIEQUIVALENTS) FOUR HOURS AFTER WATER LOAD ($M \pm m$; $n = 6$)

Indices Studied	Groups	Normal Motor Regimen	Hypokinesia		Normal Motor Regimen
		Background Period	2nd Day	27th Day	Recovery 2nd Day
% of fluid elimination	+6	104±13.2	88±11.5	116±4.7	86±12.0
	-2	107±6.9	96±8.1	103±8.5	82±7.8
	-6	113±10.7	96±11.3	107±8.0	82±8.1
	Control*	99±3.7			94±8.4
Sodium	+6	41.4±12.59	49.9±4.14	39.9±3.87	29.8±6.97
	-2	56.0±13.49	60.3±2.35	50.9±4.95	20.2±3.71
	-6	63.7±9.45	79.0±9.06	42.9±8.87	16.1±2.70
	Control*	41.6±3.65			40.7±14.48
Potassium	+6	23.4±5.1	30.2±4.29	39.4±1.78	17.5±3.39
	-2	24.5±4.3	27.0±1.75	37.6±4.34	16.4±2.31
	-6	28.3±3.0	26.1±4.04	30.8±3.98	13.1±1.58
	Control*	22/4±2.11			20.8±6.45

*Control -- subjects in a normal motor regimen during the same period of investigation

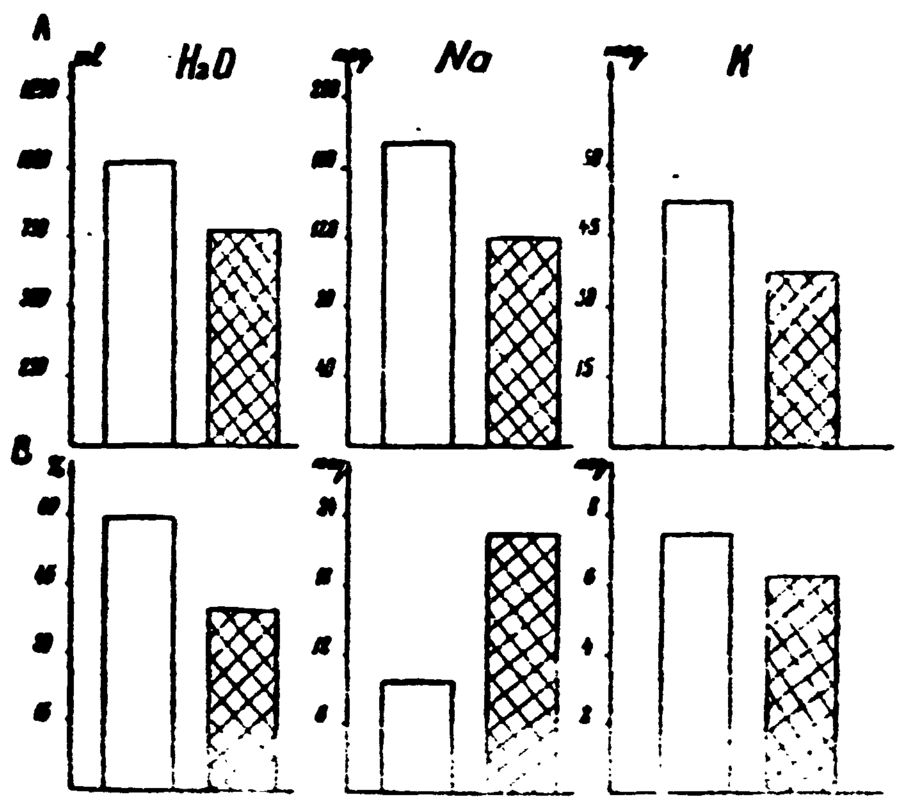

Fig. 7. Excretion of fluid, sodium, and potassium by kidneys one day (A) and two hours after water load (B).

-- before flight -- after flight

be thought even a short-term weightless condition or an aggregate of the action of a number of flight factors causes a characteristic reaction of the water-salt exchange which differs from the reaction during the simulation actions [we] applied.

Doubtless the most significant would be an evaluation of the condition of the endocrine glands both under space-flight conditions and in the study of the causes of the altered reaction of the kidney in the water test in the post-flight period. In the literature, there are data on increased daily excretion of ADH after flight (Ref. 2), and the excretion rate of corticosteroids (Ref. 1), aldosterone, angiotenzine, and catecholamines (3). At the same time, for complete evaluation of the influence of endocrine factors on the kidneys it would not be enough to know only the magnitude of the separation of hormones from urine or their concentration in the blood, while not carrying out simultaneous research on the dynamics of secre- /12 tion, exchange of hormones, and the development of sensitivity to them in cells of the effector. The necessity for a complex evaluation of the state of the endocrine system is shown by data on the influence of the ADH preparation pituitrine P on the water balance of investigators. A single injection of pituitrine even in large doses of 5000 units (for comparison let us suppose that the daily secretion of ADH in a person with moderate dehydration amounts to several hundred units) did not significantly affect the daily excretion of water and osmotically active substances (Ref. 15). This indicates that in the course of the period of research, the organism was able to compensate for changes caused by the activity of a hormone and observed over a comparatively short time.

Some information on the state of the water-salt exchange during the simulation of space-flight factors can be obtained from data of experiments in which the activity of the kidneys was studied in load tests on other functional systems — physical loading and lower-body negative pressure. In both cases, shifts of the same type in the functioning of the kidneys were observed — a decrease in glomerular filtration, a lessening of diuresis and excretion of sodium and potassium

(Table 6). The reason for this phenomenon probably can be found in the change in inflow of blood into the central portions of the vascular system which causes a change in the functioning of the kidneys according to the Henry-Gauer reflex type (Ref. 16).

Thus, these results make it possible to conclude that space flight causes a number of changes in the water-salt exchange. First to be pointed out is the decrease in the excretion of water by the kidney, regardless of refilling of water losses caused by flight, and a lowered capability to reabsorb sodium in these situations. This mismatching of the water-salt exchange regulation systems, which became evident through a functional test, is not imitated in any of the applied simulation experiments applied. In our opinion, the reason for the observed shifts is a change in the interconnection between the activity of the osmo- and volume-regulation systems connected with the transfer of their weightless state into terrestrial gravitation.

TABLE 6

INFLUENCE OF PHYSICAL LOAD AND LBNP ON ELIMINATION OF FLUIDS SODIUM AND POTASSIUM AND THE RATE OF GLOMERULAR FILTRATION ($M \pm m$; $n = 8$)

Indices Investigated	Physical Load		I	LBNP		II
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
Diuresis (ml/min)	0.95±0.08	0.60±0.1	0.84±0.04	0.79±0.08	0.88±0.1	0.69±0.08
Excretion of Sodium (microequiv/min)	138±13	105±9	135±17	148±20	142±11	105±10
Excretion of Calcium (microequiv/min)	50±4	31±8	45±12	46±7	50±6	30±6
Glomerulous Filtration (ml/min)	110±7	78±8	124±18	110±9	108±10	80±8

Note: Physical load:

The maximal endured, beginning with 600 kgm with an increase of 100 kgm each minute

ODNT:

I 25 mm Hg for 2 min; 35 mm Hg for 3 min; 40 mm Hg for 5 min; and 50 mm Hg for 5 min

II 15--50 mm Hg up to 140 min during the day according to the scheme.

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